REMARKS / ARGUMENTS

Support for Amendments

Each amendment is supported throughout the application as originally filed including the specification and drawings and includes no new matter. Exemplary passages are provided in support for amendments.

Claim 2 was amended to correct a typographical error.

Claim 8 is amended to include all elements of canceled claim 7. More specifically claim 8 recites that the biocompatible porous membrane, *comprises glass, sapphire, silicon, silicon dioxide on silicon, or one or more polymers and further wherein the thickness of said membrane.* Support may be found in original claim 7. Support may further be found in paragraph [0020], which recites, "The biocompatible porous membrane may include a nonconductive material. The nonconductive material may be glass, sapphire, silicon, silicon dioxide on silicon, or one or more polymers. In a preferred embodiment, the biocompatible porous membrane has a thickness between 2 microns and 500 microns."

Claim 11 is amended to correct a typographical error.

Claim 25 is amended to recite, *further wherein the thickness of said membrane is from 2 microns to 500 microns.* Support may be found in paragraph [0020], which recites, in part, "In a preferred embodiment, the biocompatible porous membrane has a thickness between 2 microns and 500 microns."

Claim 43 is amended to recite, *wherein the device separates an upper chamber from a lower chamber of the fluid container.* Support may be found in paragraph [00137], which recites in part, "An apparatus of the present invention that comprises an

upper chamber and a lower chamber separated by a device of the present invention can be made by any suitable methods."

Claim 50 is amended to include all elements of previous claim 49. More specifically claim 50 is amended to recite, *said two or more electrodes comprise at least four electrodes*. Support for Claim 50 may further be found in paragraph [0142], which recites,

> "In some preferred embodiments of the present invention, a device for measuring the electrical impedance, resistance, or capacitance of a cell/substrate interface, comprises four or more electrodes fabricated on the same side of a biocompatible membrane that comprises at least one pore, in which at least one surface of said biocompatible membrane allows the attachment of one or more cells. The four or more electrodes are preferably arranged in an electrode array (or an electrode structure array) that comprises two or more IDESs or CCESs, each or which comprises at least two electrodes."

Claim 51 is amended to recite, *wherein the exposed surface area of said one side of said biocompatible membrane on which electrodes are fabricated comprises an approximately uniform distribution of electrodes or electrode elements.* Support may be found in paragraph [0113], which recites, "Preferably, the distribution of electrodes or electrode elements over the sensor area is uniform or approximately uniform".

Claim 62 is amended to recite *wherein said at least one pore has a diameter of between 1 micron and 30 microns.* Support may be found in paragraph [00106], which recites in part, "For example, the membrane can comprise multiple holes of a same size that are, for mammalian cancer, epithelial, or endothelial cells, between about 1 micron and about 30 microns in diameter, more preferably between about 2 microns and about 10 microns in diameter."

Claim 65 is amended to recite that the membrane may comprise *a layer of epithelial or endothelial cells, or a combination thereof.* Support may be found in paragraph [00147], which recites in part, "In these aspects, the pores of the biocompatible membrane have a diameter of less than about 5 microns, preferably less than about 1 micron, and the upper side of the membrane preferably comprises a layer of epithelial or endothelial cells."

Claims 68 and 69 are amended to include the elements of canceled claim 67. More specifically claims 68 and 69 recite, *wherein said device is used to assay the migration or invasiveness of one or more cells.*

Claim 138 is newly added and recites, *wherein the electrodes are disposed on the surface of the membrane in the lower chamber.* Support may be found in paragraph [0018] which recites, in part, "The electrodes may be disposed on the surface of the membrane in the lower chamber."

Claim 139 is newly added and recites, *wherein the at least two electrodes that have substantially the same surface area are in an interdigitated or a concentric configuration.* Support may be found in paragraph [00112], which recites, in part, "In some preferred embodiments of the present invention, electrode structures can be interdigitated electrode structures (IDESs) or concentric electrode structures (CCESs), such as those depicted in Figures 15A and 15F."

Claim 140 is newly added and recites, *wherein the at least two electrodes have a geometry selected from the group consisting of circle-on-line, diamond-on-line, castellated, and sinusoidal geometries.* Support may be found in paragraph [00112], which recites, in part, "Examples of such large perimeter structures are a diamond-on-line electrode structures, circle-on-line electrode structures shown in Figures 15C, castellated electrode structures as shown in Figure 15B and 15D." Further support may be found in paragraph [00127], which recites, in part, "In yet another example, the electrode(s) can have a shape of a rectangle, a circle, a circle on a rectangular line or a sinusoidal line."

Claim 141 is newly added and recites, *wherein the width of the electrodes is from 20 microns to 500 microns; further wherein the gap between electrode elements is between 3 microns and 80 microns in width; further wherein the ratio of the gap width to the electrode element width ranges from about 1:20 to about 3:1; further wherein the gap between electrode elements is between about 0.2 time and about 3 times the width of cells used in the measuring electrical impedance, resistance or capacitance of a cell/substrate interface.* Support may be found in paragraph [00115], which recites in part,

> "While other gap dimensions may be used, preferably, the gap between electrode elements of the electrode structures ranges from about 0.2 times and 3 times the width of an average cell used in an assay using the device. Preferably, the width of a gap between electrodes or electrode elements of a device of the present invention used for monitoring eukaryotic cells, such as mammalian cells, such as cancer cells, endothelial or epithelial cells, is between about 3 microns and 80 microns, more preferably between about 5 microns and 50 microns, and most preferably between about 8 microns and 30 microns."

Further support may be found in paragraph [00117], which recites in part, "More preferably, the electrode width is in the range between 20 micron and 500 micron." Even further support may be found in paragraph [00117], which recites in part, "While other ratios of the electrode element width to gap may be utilized, preferably, the ratio of electrode element width to gap width is between about 1:3 and 20:1."

Claim 142 is newly added and recites, *The device of Claim 51, further comprising an impedance analyzer connected to the electrodes.* Support may be found in paragraph [0019], which recites, "In a preferred embodiment, the device includes an impedance analyzer in electrical communication with the electrodes."

Claim 143 is newly added and recites, *An apparatus for measuring electrical impedance, resistance, or capacitance of a cell/substrate interface, comprising a plate that comprises one or more wells, at least one of which comprises the device of Claim 24, wherein each device separates each well into upper and lower chambers.* Support may be found in paragraph [00137], which recites in part, "An apparatus of the present

invention that comprises an upper chamber and a lower chamber separated by a device of the present invention can be made by any suitable methods." Support may further be found in paragraph [0162], which recites,

> "The present invention also includes apparatuses for measuring electrical impedance, resistance, or capacitance of a cell/substrate interface, comprising a plate that comprises two or more wells, each of which comprises a membrane that comprises at least two electrodes and one or more pores, where the membrane separates a well into upper and lower chambers, and the membrane comprises a surface suitable for cell attachment and growth."

Claim 144 is newly added and recites, *wherein the two or more electrodes are on the lower side of the membrane.* Support may be found in paragraph [00155], which recites, "In other aspects of these embodiments, the electrodes are fabricated on the lower side of the membrane."

Claim 145 is newly added and recites, *wherein the two or more electrodes are on the upper side of the membrane and wherein the pores of the biocompatible membrane have a diameter of less than 5 microns.* Support may be found in paragraph [00147], which recites in part, "In some aspects of the present invention, the electrodes are fabricated on the upper side of the membrane. In these aspects, the pores of the biocompatible membrane have a diameter of less than about 5 microns, preferably less than about 1 micron, and the upper side of the membrane preferably comprises a layer of epithelial or endothelial cells."

Claim 146 is newly added and recites, *wherein the biocompatible membrane is reversibly or irreversibly attached to a first plate that comprises two or more wells that provide lower chambers of cell migration units and is reversibly or irreversibly attached to a second plate that provides tube structures that provide upper chambers of cell migration units, such that each cell migration unit comprises a single IDES or CCES.* Support may be found in paragraph [00157], which recites in part,

> "The present invention includes apparatuses for measuring electrical impedance, resistance, or capacitance of a

> cell/substrate interface in which a biocompatible membrane comprising two or more electrodes is reversibly or irreversibly attached to a first plate that comprises two or more wells that provide lower chambers of cell migration units and is reversibly or irreversibly attached to a second plate that provides tube structures that provide upper chambers of cell migration units (such as a bottomless micro-well plate), such that each cell migration unit comprises a single IDES or CCES."

Claim 147 is newly added and recites, *wherein said membrane comprises a layer of cells on the upper side of the membrane, wherein said cells are epithelial cells or endothelial cells.* Support may be found in paragraph [00147], which recites in part,

> "In some aspects of the present invention, the electrodes are fabricated on the upper side of the membrane. In these aspects, the pores of the biocompatible membrane have a diameter of less than about 5 microns, preferably less than about 1 micron, and the upper side of the membrane preferably comprises a layer of epithelial or endothelial cells."

Claim 148 is newly added and recites, *An apparatus according to Claim 144, further comprising an insert tray that comprises one or more insert chamber, each of which comprising: (a) fluid impermeable walls, and (b) the device of Claim 24 forming the bottom of each of said one or more insert chamber; wherein each insert chamber fits into a well of said plate such that the wells of the plate form a lower chamber and the insert forms an upper chamber of a cell invasion/migration unit.* Support may be found in paragraph [00169], which recites,

> "The present invention also comprises apparatuses for measuring electrical impedance, resistance, or capacitance of a cell/substrate interface, comprising an inert tray that comprises one or more insert chambers, each of which comprises fluid impermeable walls and a porous biocompatible membrane comprising two or more electrodes forming the bottom of at least one, of the one or more insert chambers. Preferably the apparatus also includes a plate that comprises one or more wells, such that an insert tray of the present invention fits the plate. Preferably, the insert tray comprises multiple insert chambers and a corresponding plate comprises multiple

> wells, and the insert tray is designed such that the insert chambers align with and fit into the wells of a plate. Each insert chamber fits preferably into a well of a plate such that the wells of the plate form lower chambers and the inserts of an insert tray form upper chambers of a cell invasion/migration unit."

Claim 149 is newly added and recites, *The apparatus according to Claim 146, further comprising an impedance analyzer, interface electronics comprising electronic switches to control and switch said impedance analyzer to different electrode structure units of said apparatus, and a software that can enable real time measurement or monitoring of impedance between the electrodes or electrode structures of said apparatus.* Support may be found in paragraph [00174], which recites

> "In preferred embodiments of the present invention, a system that comprises an insert tray and multi-well plate apparatus of the present invention also includes interface electronics, including impedance measurement circuit and switches (e.g. electronic switches), to control and switch the impedance measurement circuits to different electrode structure units of the apparatuses of the present invention."

Further support may be found in paragraph [00129], which recites in part, "Preferably, a system of the present invention also includes a computer having software programs that can enable real-time measurement or monitoring of impedance between the electrodes or electrode structures of the apparatuses of the present invention."

Claim 150 is newly added and recites, *The apparatus according to Claim 149, wherein said software has at least one function selected from the group consisting of: (a) controlling electronic switching for connecting said impedance analyzer to one of multiple electrode structure units of the present apparatuses; (b) controlling impedance analyzer for measurement of impedance between or among electrode structures at one or multiple frequencies; (c) processing the acquired impedance data to derive appropriate biologically relevant parameters (e.g., cell number index); (d) displaying the results on a monitor or storing results; and (e) automatically performing above functions (a) through (d) at regular or irregular time intervals.* Support may be found in paragraph [00130], which recites,

> "Preferably, the software program has one or more of the following functions: (1) electronically switching for connecting impedance measuring circuit (or analyzer) to one of multiple devices of the present apparatuses; (2) controlling impedance measurement circuit (or analyzer) for measurement of impedance between or among electrodes or electrode structures at one or multiple frequencies; (3) processing the acquired impedance data to derive appropriate biologically relevant parameters (e.g., cell number index, or cell migration index); (4) displaying the results on a monitor or storing results; (5) automatically performing above functions 1 through 4 at regular or irregular time intervals."

Claim 157 is newly added and recites, *A method for monitoring cell migration or invasion, comprising: a) providing an apparatus of claim 144; b) placing cells in the upper chamber of said apparatus ; and c) monitoring a change of impedance between or among the electrodes to monitor migration or invasion of said cells.* Support may be found in paragraph [00175], which recites

> "The present invention also includes methods for monitoring cell migration or invasion, comprising providing an apparatus as described above for cell migration or invasion, placing cells in the upper chamber of said apparatus; and monitoring a change of impedance between or among the electrodes to monitor migration or invasion of the cells."

Claim 158 is newly added and recites, *The method according to Claim 157, further comprising adding a known or suspected modulator of cell migration or cell invasion to the lower chamber of said apparatus.* Support may be found in paragraph [0024], which recites, "The method may also include introducing a known or suspected modulator of cell migration to the lower chamber of the device."

Claim 159 is newly added and recites, *The method according to Claim 157, further comprising adding a known or suspected modulator of cell migration or cell invasion to the upper chamber of said apparatus.* Support may be found in paragraph [0025], which recites, "In another embodiment, the method includes introducing a known or suspected modulator of cell migration to the upper chamber of the device."

I. Response to Claim Rejection Under 35 U.S.C. §112

The Examiner has rejected claims 60 and 61 under 35 U.S.C. §112, second paragraph, as being indefinite. More specifically the Examiner has noted that "said layer of epithelial cells or endothelial cells" lacks antecedent basis. Applicants have canceled claims 60 and 61 to economize on USPTO fees.

Applicants respectfully request the rejections be withdrawn.

II. Response to Claim Rejections Under 35 U.S.C. §103

A. Claims 1-11, 24, 25, 28, 29, 32 and 49 are not obvious over either Picard (US 2004/0091397) or Tchao (US 5,601,997) in view of Lynes et al (US 6,723,523)

The Examiner has rejected Claims 1-11, 24, 25, 28, 29 and 49 under 35 U.S.C. §103(a) over Picard or Tchao in view of Lynes. More specifically, the Examiner alleges both Picard and Tchao disclose devices for monitoring the migration or invasion of biological particles. The Examiner argues that Picard discloses an upper chamber (114); a lower chamber (116); a biocompatible porous membrane (106) having a porosity sufficient to allow cells to migrate there through and the membrane (106) separates the upper and lower chambers (see Fig. 1 B). Similarly, the Examiner argues Tchao discloses an upper chamber (24); a lower chamber (22, 28); a biocompatible porous membrane (10) having a porosity sufficient to allow cells to migrate there through and the membrane separates the upper and lower chambers (See Fig. 2).

With respect to claim 1, the Examiner argues while both of the references of Picard and Tchao disclose the use of optical detection devices (see sensor 120 of Picard and detector 30 of Tachao) for detecting the presence of cells within the lower chamber, the references do not disclose that at least two electrodes are present in the lower chamber for detecting the presence of cells by a change in impedance between electrodes. However, the Examiner argues Lynes discloses that it is known in the art to employ

impedance sensing electrodes within a cell or culture space for detecting the presence and/or movement of a cell in response to a chemotactic gradient (See col. 9, ll. 55-67).

Therefore the Examiner argues that it would have been obvious to one of ordinary skill in the art to replace the optical detection systems of the primary references with an impedance measurement system suggested by the reference of Lynes for the known and expected result of providing an alternative means recognized in the art to detect or sense the presence of cells within the lower chambers of the test devices.

Applicants' Response

Claim 1 is not obvious over Picard or Tchao in view of Lynes. More specifically, Lynes "builds on a standard configuration of the ECIS system of Giaever and Keese." (Col. 9, ll. 55-57) In the standard ECIS system, "two electrodes are lithographed..." (Col. 3, ll. 45-55) and there are two electrodes, one being the sensing electrode and one being the counter electrode. Importantly, "In an ECIS system, the relative size of the sensing and counter electrodes can be significant. With large sensing electrodes, cell-related resistance signals become difficult to detect." (Col. 4, ll. 27-30) In addition, "When electrodes have a surface area of approximately 10^{-3} cm^2 or less, the impedance of the electrode-electrolyte interface at 4kHZ predominates, and in this situation, changes in resistance due to interaction of the cells with the electrode surface are clearly revealed." (Col. 4, ll. 32-37) "Due to the relative small size of the [sensing] electrode, resistance at the sensing electrodes predominates in the system." (Col. 3, ll. 63-65) In summary, the Lynes system operates by combining a small sensing electrode having a relatively small resistance with a large counter electrode "such that resistance at the sensing electrodes predominate." Thus, the device in Lynes operates by detecting changes at the sensing electrode.

In contrast, Applicants invention does not utilize a small sensing electrode and a larger counter electrode system as described in Lynes. Applicants' invention includes at least two electrodes where cells contacting either electrode can result in an impedance change. In other words, all electrodes may be used to monitor impedance.

The structural distinctions between Applicants' electrodes and Lynes sensing-counter electrode system would result in significantly different methods of operation if

Lynes were adapted to a migration or invasion test. More specifically, if Lynes were adapted to such an assay, impedance would only be measured when contact between a cell and the sensing electrode occurs because "resistance at the sensing electrodes predominates in the system"; whereas Applicants' invention detects changes in impedance when cells contact either of the two electrodes.

In addition, the Lynes' system includes a "chemical gradient stabilizing medium in the form of an agarose layer **64**" (Col. 9, ll. 60-61) for "establishment of a chemotactic gradient between the one or more chemical gradient volumes **66** loaded with chemoattractant and the cell containment volumes **68** in which cells are initially loaded." (Col. 9, ll. 63-66) "Due to the unique, art-recognized physical and chemical properties of a medium such as agarose, the resulting chemical gradient that is sensed by the cells in the cell containment volume comprises a greater volume and persists for a much longer time than the type of gradient that exists in the prior art Boyden-type chemotactic assay." (Col. 10, ll. 4-10) Thus, the Lynes sensing-counter electrode system requires a "chemical gradient stabilizing medium."

In contrast, Applicants' invention does not require such a "chemical gradient stabilizing medium."

The Lynes system also includes one or more "cell containment volumes" (Col. 5, ll. 10-30) and one or more "chemical agent volumes" (Col. 5, ll. 10-30) with "a biocompatible chemical gradient establishing medium in simultaneous diffusional contact with the arrays of cell containment volumes and chemical agent volumes" (Col. 5, ll. 25-28). Furthermore, "an array of one or more chemical agent volumes" are "interspersed among the array of one ore more cell containment volumes" (Col. 5, ll. 14-16) and "at least one of the sensing electrodes is between one cell containment volume and one chemical agent volume" (Col. 5, ll. 18-20). In addition, "Assuming as a first principle that the dimension of cell containment and chemical agent vilumes are significantly smaller than the respective distances separating them from the one or more sensing electrodes, it is possible to treat the cell containment volumes and the chemical agent volumes as point sources from the species that diffuse from them. (Col. 10, ll. 64-67, Col. 11, ll. 1-3) Thus, the system operates as a radial diffusion system where the chemical agent diffuses away from a point source in a radial fashion.

In contrast, Applicants' invention does not utilize "chemical agent volumes interspersed among cell containment volumes", and does not utilize a radial diffusion system. Applicants' invention includes an upper chamber, a lower chamber and biocompatible porous membrane. Cell migration through the biocompatible membrane may be influenced by cellular properties, pore size and distribution and compounds or other agents applied to the top or bottom chambers.

Applicants agree with the Examiner that neither Picard nor Tchao disclose the use of electrodes in the detection of cells. Picard provides a two chamber system separated by a membrane. Cells are optically detected on the surface of the lower chamber. More specifically referring to FIG. 1B, the cells **122** are detected at the bottom surface **112** of the lower well **108**.

Tchao is a two chamber system separated by a radiation opaque membrane. Cells labeled with a dye, such as a fluorescent dye, are placed in a first chamber and a chemoattractant in a second chamber. The cells migrate through pores of the opaque membrane and radiation is measured from the side of the opaque membrane closest to the second chamber. (see Col. 2, ll. 43-65) Referring to Col. 3, ll. 65-67, "As seen in FIG. 2, a space **28** is created between the radiation opaque membrane **10** and the bottom of the well **22**." Now referring to Col. 2, ll. 18-21, "With the preferred apparatus illustrated in FIGS. 1 and 2, this step would comprise stimulating and measuring the radiation from below the radiation opaque membrane, that is through space **28**". Thus, the device disclosed in Tchao measures radiation (such as fluorescence) from a bottom second chamber.

It is not clear how one combines Lynes and Picard or Lynes and Tchao. For example, it is not clear where the "chemical gradient stabilizing medium" would be placed in the combined system. It is not clear where "chemical agent volumes" that are "interspersed among cell containment volume" would be placed in the combined system. It is not clear where "the sensing electrodes and large counter electrodes" would be placed in the combined system. It is not clear how one achieves that "at least one sensing electrodes is between one cell containment volume and one chemical agent volume".

Applicants do not utilize a sensing-large counter electrode system as described by Lynes, do not utilize "chemical gradient stabilizing medium" as described by Lynes, do

not utilize "chemical agent volumes" that are "dispersed among cell containment volumes", do not utilize an optical system as described by Picard or a radiation detecting system as described by Tchao. Claim 1 is therefore not obvious over Picard or Tchao in view of Lynes.

With respect to claims 2-11, Applicants' incorporate the arguments setforth above as claims 2-11 depend from claim 1.

With respect to claims 24, 25, 28 and 29, Applicants' incorporate the arguments setforth above with respect to Lynes requires a sensing electrode and counter electrode system; whereas Applicants' invention includes two or more electrodes fabricated on one side of a biocompatible membrane that comprises at least one pore, wherein said device has a surface suitable for cell attachment or growth.

Claim 24 is not obvious over Picard or Tchao in view of Lynes. Lynes does not teach, mention or discuss anything relating to a device comprising two or more electrodes fabricated on a biocompatible membrane that comprises at least one pore, wherein said device has a surface suitable for cell attachment or growth. Even putting Picard or Tchao's invention together with Lynes', because of very different devices and different approaches employed by Lynes, it is not obvious to produce Claim 24 devices, that comprises two or more electrodes fabricated on biocompatible membrane that comprises at least one pore, wherein said device has a surface suitable for cell attachment or growth. Furthermore, as for the combination of Lynes and Picard or Lyne and Tchao, it is not clear how one combines Lynes and Picard or Lynes and Tchao. For example, it is not clear where the "chemical gradient stabilizing medium" would be placed in the combined system. It is not clear where "chemical agent volumes" that are "interspersed among cell containment volume" would be placed in the combined system. It is not clear where "the sensing electrodes and large counter electrodes" would be placed in the combined system. It is not clear how one achieves that "at least one sensing electrodes is between one cell containment volume and one chemical agent volume".

Referring to Col. 10, ll. 21-30 of Lynes,

> "The cells loaded into the one or more cell containment volumes begin to move under the influence of the gradient established by diffusion of the chemoattractant species over the substrate **58** and under the agarose layer **64** in the direction of the gradient and interact with the one or more sensing electrodes **10** in their path. The cells eventually reach and move across the sensing electrode **10** located, in a preferred embodiment between the cell containment volume **68** and the chemical agent volumes **66** as illustrated in panel B of FIG. 2."

FIG. 2 of Lynes displays a sensing electrode **10** and a large counter electrode **40** placed on a substrate **58.** The sensing electrode is positioned between the cell containment volume **68** and chemical agent volume **66**. The agarose is positioned above the substrate for radial diffusion of the chemoattractant (across and parallel to the substrate). The cell traverses across the top of the sensing electrode when migrating along the bottom of the well or substrate. Lynes requires the use of a sensing electrode and a large countere electrode, the use of "chemical agent volumes" that are "interspersed among the array of one or more cell containment volumes" (Col. 5, ll. 14-16), the use of "biocompatible chemical gradient stabilizing medium" (Col. 5, ll. 25-27). In contrast, the present invention includes two or more electrodes fabricated on a biocompatible membrane that includes at least one pore, wherein the device has a surface suitable for cell attachment or growth.

Picard provides a two chamber system separated by a membrane. Cells are optically detected on the surface of the lower chamber. More specifically referring to FIG. 1B, the cells **122** are detected at the bottom surface **112** of the lower well **108**.

Tchao is a two chamber system separated by a radiation opaque membrane. Cells labeled with a dye, such as a fluorescent dye, are placed in a first chamber and a chemoattractant in a second chamber. The cells migrate through pores of the opaque membrane and radiation is measured from the side of the opaque membrane closest to the second chamber. (see Col. 2, ll. 43-65) Referring to Col. 3, ll. 65-67, "As seen in FIG. 2, a space **28** is created between the radiation opaque membrane **10** and the bottom of the well **22**." Now referring to Col. 2, ll. 18-21, "With the preferred apparatus illustrated in

FIGS. 1 and 2, this step would comprise stimulating and measuring the radiation from below the radiation opaque membrane, that is through space **28**". Thus, the device disclosed in Tchao measures radiation (such as fluorescence) from a bottom second chamber.

As for the combination of Lynes and Picard or Lynes and Tchao, it is not clear how one combines Lynes and Picard or Lynes and Tchao. For example, it is not clear where the "chemical gradient stabilizing medium" would be placed in the combined system. It is not clear where "chemical agent volumes" that are "interspersed among cell containment volume" would be placed in the combined system. It is not clear where "the sensing electrodes and large counter electrodes" would be placed in the combined system. It is not clear how one achieves that "at least one sensing electrodes is between one cell containment volume and one chemical agent volume".

The present invention Claim 24 includes two or more electrodes fabricated on one side of a biocompatible membrane having at least one pore wherein the device is suitable for cell attachment or growth. Moreover Applicants' Claim 24 does not utilize the sensing and large counter electrode approach as provided by Lynes, do not utilize "chemical gradient stabilizing medium" as described by Lynes, do not utilize "chemical agent volumes" that are "dispersed among cell containment volumes", do not utilize an optical system as described by Picard or a radiation detecting system as described by Tchao.

To summarize, Lynes, Picard and Tchao do not disclose the elements of claim 24 nor would the combination of Lynes, Picard and Tchao provide the technology disclosed in claim 24.

Further with respect to claim 25, Applicants' have added "further wherein the thickness of the membrane is from 2 microns to 500 microns." These elements (two or more electrodes fabricated on a biocompatible membrane that comprises at least one pore) are not provided in Picard, Tchao or Lynes. Even though Lynes discloses a device for measuring cell chemotactic activity with impedance detection, the device, the approach, the factors influencing the experimental results are very different from Applicants' invention, as described above.

With respect to claims 32 and 49, Applicants' have cancelled claims 32 and 49 to economize on USPTO fees. However, Applicants' arguments previously setforth would have also applied with respect to claims 32 and 49.

Applicants respectfully request the rejections of claims 1-11, 24, 25, 28, 29, 32 and 49 be withdrawn.

B. Claims 9, 24, 25, 28, 29, 30, 32 and 60-69 are not obvious over Picard (US 2004/0091397) or Tchao (US 5,601,997) in view of Lynes et al (US 6,723,523) taken further in view of Springer et al (US 5,514,555)

The Examiner has rejected claims 9, 24, 25, 28, 29, 30, 32 and 60-69 under 35 U.S.C. §103(a) over Picard or Tchao in view of Lynes in further view of Springer.

Applicants' Response

Applicants have canceled claims 30, 32, 60, 61, 63, 64, 66, and 67 to economize on USPTO fees. Claim 9 depends from claim 1 and claims 25, 28, 29, and 62, 68 and 69 depend from Claim 24. Thus Applicants incorporate the arguments setforth above with respect to claim 1 and claim 24. Springer does not disclose the deficiencies provided above with respect to claims 1 or 24.

Thus, Applicants respectfully request the rejections be withdrawn.

C. Claims 36, 43, 44, 50 and 51 are not obvious under 35 USC §103(a) over Picard (US 2004/0091397) or Tchao (US 5,601,997) in view of Lynes et al (US 6,723,523) taken further in view of Ehret et al (Biosensors)

The Examiner has rejected claims 36, 43, 44, 50 and 51 over Picard or Tchao in view of Lynes and in further view of Ehret. Applicants have canceled claim 44 to economize on USPTO fees. Claims 36, 43, 50 and 51 depend from claim 24. Applicants' incorporate the arguments provided above with respect to claim 24. Again, even though Ehret does disclose interdigitated electrodes for impedance detection and even though Lynes disclose a device for measuring cell chemotactic activity with

impedance detection, because of very different devices and approaches employed by Lynes as described above, it is not obvious to produce Claim 24 devices, that comprises two or more electrodes fabricated on biocompatible membrane that comprises at least one pore, wherein said device has a surface suitable for cell attachment or growth.

Thus, Applicants respectfully request the rejection of claims 36, 43, 44, 50 and 51 be withdrawn.

III. Conclusion

Applicants respectfully request all rejections be withdrawn and request an allowance be granted for the present application.

Respectfully submitted,

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